

REMARKS

Claims 1, 3-10 and 16-23 were and are still pending in this application. Claim 1 has been amended to clarify claim language. No new matter has been added.

Rejections under 35 USC §103

Claims 1, 3-10, and 16-23 are rejected under 35 USC §103(a) as being obvious over *Oeltgen et al* (US 6,645,938) in view of *Motterlini et al* (Circulation Research, 2002). The Examiner asserts that *Oeltgen et al* teaches methods and compounds for protecting organs against ischemia and reperfusion injury. The Examiner admits that *Oeltgen et al* does not teach a preservative solution comprising a metal carbonyl compound which makes available carbon monoxide. The Examiner alleges that "this deficiency is cured by the teachings of *Motterlini et al*". According to the Examiner, *Motterlini et al* teaches that "[Ru(CO)₃Cl₂]₂ dissolved in DMSO releases CO into the solution" and "CO releasing compounds have been found to be pivotal in the defensive system against ischemia-reperfusion damage. (see page 17, column 1, paragraph 1)."

Applicant respectfully disagrees. *Oeltgen et al* teaches that a peptide compound ("compound-D") may be used in a preservative solution for protecting against ischemia and reperfusion injury of mammalian organs. According to *Oeltgen et al*, compound-D may work by opening or activation of K_{ATP} channels (column 6, lines 20-21). *Oeltgen et al* does not teach or suggest modifying compound-D or using compounds other than compound-D. *Oeltgen et al* does not provide one of ordinary skill in the art with a reason or motivation to use a compound(s) other than compound-D to produce the same effect.

However, and for arguments sake, if *Oeltgen et al* was to provide one of ordinary skill in the art with a reason or motivation to try or investigate a compound(s) other than compound-D, the reasonable choice based on the teachings of *Oeltgen et al* would be other peptide compounds, or possibly small organic molecules (e.g., peptidomimetics) which have the same pharmacological effect as peptide compound D. One of ordinary skill in the art would or have no reason or motivation to try or investigate the effects of carbon monoxide (CO) on ischemia and reperfusion injury. It was not known, and *Oeltgen et al* does not teach or suggest, that CO has any effect on the

opening of K_{ATP} channels. One of ordinary skill in the art would have even less reason to consider trying metal carbonyl compounds, such as those used in the present invention, as a source of CO.

Contrary to the Examiner's assertion, the teachings of *Motterlini et al* do not cure the deficiency in *Oeltgen et al*. *Motterlini et al* discloses a class of metal carbonyl compounds which are capable of releasing CO. However, it does not teach or suggest that these compounds could be used to treat or prevent ischemic or reperfusion injury nor does it teach or suggest that the released CO has any effect on K_{ATP} channels.

The passage of *Motterlini et al* cited by the Examiner (page 17, column 1, paragraph 1), refers to the role of heme oxygenase (HO-1), an endogenous biological molecule, as a defensive system against stressful stimuli such as ischemia-reperfusion damage:

“The main endogenous source of CO is heme oxygenase, which exists in constitutive (HO-2 and HO-3) and inducible (HO-1) isoforms; heme serves as substrate for HO-1 and HO-2 in the formation of CO, free ferrous iron, and biliverdin, the latter being rapidly converted to bilirubin by biliverdin reductase. There is general consensus, supported by extensive published reports, that HO-1 represents a pivotal inducible defensive system against stressful stimuli, including UVA radiation, carcinogens, ischemia-reperfusion damage, endotoxic shock, and several other conditions characterized by production of oxygen-derived free radicals.”

The Examiner has generalized this into a statement that “*Motterlini et al* teach that CO releasing compounds have been found to be pivotal in the defensive system against ischemia-reperfusion damage”. This is not taught or suggested by *Motterlini et al* and the Examiner's generalization is not justified.

The Examiner also asserts that *Motterlini et al* teaches that “the transition metal carbonyls taught are useful for defense against ischemia-reperfusion damage”. There is no basis in the disclosure of *Motterlini et al* to support the Examiner's assertion. *Motterlini et al* does not teach or suggest that the synthetic metal carbonyls under investigation could be used in a composition for protecting an isolated organ from damage. *Motterlini et al* focuses on the vasodilatory effects of these metal carbonyl compounds and suggests their use to alleviate vascular and immuno-related dysfunctions (see abstract).

The instant application is the first demonstration that carbon monoxide released *in vivo* by metal carbonyl compounds, can effectively prevent ischemic injury. Without the information provided in the present application, one of ordinary skill in the art would not consider using metal carbonyl compounds in a composition for protection of an extracorporeal organ or an isolated organ that is inside or attached to the body.

The Examiner has not provided a clear and reasonable argument why one of ordinary skill in the art would use the metal carbonyl compounds of *Motterlini et al* in a solution such as that taught by *Oeligen et al* to protect an extracorporeal organ or an isolated organ from ischemic injury let alone have a reasonable expectation of success in doing so. The only way to arrive at the Examiner's combination of these references is through the application of hindsight reconstruction of Applicant's invention based on the teachings in Applicant's specification. This is improper.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 103.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Motterlini et al., Applicant

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